Work Group report: Oral food challenge testing

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Oral food challenges are procedures conducted by allergists/immunologists to make an accurate diagnosis of immediate, and occasionally delayed, adverse reactions to foods. The timing of the challenge is carefully chosen based on the individual patient history and the results of skin prick tests and food specific serum IgE values. The type of the challenge is determined by the history, the age of the patient, and the likelihood of encountering subjective reactions. The food challenge requires preparation of the patient for the procedure and preparation of the office for the organized conduct of the challenge, for a careful assessment of the symptoms and signs and the treatment of reactions. The starting dose, the escalation of the dosing, and the intervals between doses are determined based on experience and the patient's history. The interpretation of the results of the challenge and arragements for follow-up after a challenge are important. A negative oral food challenge result allows introduction of the food into the diet, whereas a positive oral food challenge result provides a sound basis for continued avoidance of the food. (J Allergy Clin Immunol 2009;123:S365-83.)

Key words: *Oral food challenge, food allergy, food allergens, anaphylaxis, food additives, single-blind, placebo-controlled oral food challenge, double-blind, placebo-controlled oral food challenge, skin prick test, IgE, food protein–induced enterocolitis syndrome, peanut, cow's milk, milk, egg, wheat, tree nuts*

Abbreviations used
DBPCFC: Double-blind, placebo-controlled food challenge
OFC: Oral food challenge
SPT: Skin prick test

Physician-supervised diagnostic oral food challenges (OFCs), introduced in clinical practice by May 1976 in the form of double-blind, placebo-controlled food challenges (DBPCFCs), are procedures that may be used to establish definitively whether a food is the cause of adverse reactions. They are used as clinically indicated, either at initial diagnosis or during follow-up.[1-6] This article is intended to provide a practical and comprehensive guide to aid allergists/immunologists, who are uniquely qualified to perform diagnostic OFCs, in the use of the procedure for patient care in a scientifically sound, safe, and practical manner. It describes approaches used by allergists/immunologists in the United States and incorporates critically reviewed published international experience.[4,7] Additional resources are "Food Allergy: A Practice Parameter"[6] and "A Health Professional's Guide to Office Food Challenges."[8]

INDICATIONS FOR AN OFC

An OFC may be indicated to confirm that an allergic or other adverse reaction to a food or food additive exists or that it has resolved. The decision to proceed to OFC is complex and may be influenced by many factors including the patient's medical history, age, past adverse food reactions, skin prick test (SPT) and serum food-specific IgE test results, and concomitant food allergies. The decision is also influenced by the importance of the food to the patient because of its nutritional value, ubiquitous presence in the diet or ethnic diets, and the patient's and family's preferences (Box 1). OFC can clarify the status of allergy to any food including peanut, tree nuts, seeds, fish, and shellfish, which are associated with considerable anxiety because of their potential to induce life-threatening anaphylaxis.[9,10]

RISKS AND BENEFITS OF AN OFC

An OFC resulting in a clinical reaction is termed a *positive* or *failed* challenge, whereas an OFC without a clinical reaction is termed a *negative* or *passed* challenge. For the purpose of this document, the authors chose to use *positive* and *negative* terminology. There have been no associated deaths from OFC reported in the literature indexed since 1976 in PubMed (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi). However, positive OFCs have inherent risks including acute allergic reactions with potentially life-threatening anaphylaxis; exacerbation of atopic dermatitis; and emotional distress, particularly in older children, teenagers, and adults who may become more anxious about the food

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BOX 1. Indications for an OFC

Identify foods causing acute reactions for initial diagnosis of food allergy and for monitoring resolution of food allergy
Determine whether food allergens associated with chronic conditions such as atopic dermatitis or allergic eosinophilic esophagitis will cause immediate reactions
Expand the diet in persons with multiple dietary restrictions, usually because of subjective complaints such as headaches or hyperactive behavior
Assess the status of tolerance to cross-reactive foods
Assess the effect of food processing on food tolerability, eg, fruits and vegetables that may be tolerated in cooked form in the pollen-food allergy syndrome

allergy. In patients with cardiovascular disease, anaphylaxis or its treatment could result in morbidity. A possible effect of a positive OFC on preventing or delaying resolution of a food allergy has not been studied systematically. However, in the authors' experience, patients who have had 1 or several positive OFCs to a food may eventually have a negative OFC, providing evidence that a positive OFC does not necessarily prevent the resolution of the food allergy. The benefits of a positive OFC include a conclusive diagnosis of food allergy demonstrating the need for continued counseling in strict avoidance of the food, reduction of the risk of inadvertent exposures, reduction of anxiety about the unknown, and validation of the patients' and families' efforts to avoid a food. The benefits of a negative OFC are expansion of the diet and improvement of the patient's nutrition and quality of life.

REASONS FOR DEFERRING AN OFC

An OFC may be deferred if there is a high likelihood of reacting to the food as predicted by the food reaction history, whether immediate or delayed; levels of serum food-specific IgE antibody; and/or results of quantitative skin prick testing and the patient's age (Tables I and II). OFC is relatively contraindicated in conditions that increase the risk of severe anaphylaxis, such as a recent convincing anaphylactic reaction to the food or unstable asthma. It would not be recommended to perform an OFC for a patient with recent anaphylaxis to the trigger food. The length of time that may warrant reconsideration of performing an OFC may vary according to circumstances including the age of the patient, additional history, and results of testing. For example, children are more likely than adults to develop spontaneous tolerance to a food over a short period. To illustrate, a 7-year-old child with severe anaphylaxis to a food at the age of 4 years who otherwise fits the criteria of being a good candidate for an OFC may be offered an OFC. In contrast, an adult patient with the same 3-year interval since the anaphylaxis to the trigger food may be a poor candidate for an OFC.

Other reasons to defer an OFC may include confounding medical conditions and medications that may interfere with treatment of allergic reactions, such as cardiovascular disease, pregnancy, and treatment with β-blockers; and medical conditions that may preclude interpretation of the OFC, such as uncontrolled eczema and severe allergic rhinitis. In these conditions, OFCs are not suggested unless extenuating circumstances exist, especially if the OFC can be delayed until the condition resolves. However, in patients with multiple dietary restrictions, OFCs may be considered, even if the chance of a reaction is relatively high, because of the potential benefit of expanding the diet. For practical reasons, OFCs in infants and young children who may not cooperate with the feeding might be deferred until the child is older or until special arrangements are made to provide a longer time to complete the feeding and to provide an adequate observation period.

A comprehensive discussion of the diagnosis of food allergy by history, SPT, and food-specific serum IgE antibody test is beyond the scope of this article. It is to be noted that the published guidelines from the American Academy of Allergy, Asthma & Immunology/American College of Allergy, Asthma and Immunology and the European Academy of Allergy and Clinical Immunology agree that the laboratory test results are never an absolute indication or contraindication to performing an OFC and that laboratory test results need to be interpreted in the context of a clinical history of an individual patient (see Clinical Vignette).[4,6] Furthermore, current research has focused on a limited number of common food allergens in infants and children, most of whom had atopic dermatitis, with a paucity of data in adults.[6,11-14] Limited data exist to support deferring the OFC based on laboratory test results in children with few specific food allergies (cow's milk, egg, peanut, and white fish). It is not known whether the same predictive values are applicable to adults with food allergy. Serum food-specific IgE levels that are highly (90% to 95%) predictive of an allergic reaction on ingestion have been reported in children, primarily children with atopic dermatitis.[15-17] However, allergists in Europe have advocated using 99% predictive values for deferring food challenges.[18-20] The likelihood of a clinical reaction during OFC increases with higher predictive values of serum food-specific IgE and decreases gradually with lower values.[6,16,20] The mean diameter of the wheal on SPT has also been used for assessing reaction risk, with the same limitations as discussed for serum food-specific IgE levels (Table II).[17,19,21,22] It should be remembered that serum food-specific IgE levels and sizes of SPT wheals do not predict the severity of the clinical reactions.[23,24] It is well established that detection of sensitization by the presence of food-specific IgE does not always indicate clinical allergy, and reactions, including severe ones, may occur in patients with negative test results.[6,13] In general, if a patient has a negative skin test, undetectable serum food-specific IgE level, and no history of convincing symptoms of immediate food allergy (eg, symptoms limited to behavioral changes or delayed/chronic gastrointestinal symptoms), gradual home introduction of the food in question may be attempted. For those patients who have a history of convincing immediate allergic reactions to a food (within 2 hours) or who present with a history of anaphylaxis to the food in question in isolation or in a mixed meal, even in the setting of negative laboratory and skin tests, a physician-supervised OFC is needed to confirm or refute allergy to this food.

In clinical practice, young patients with estimated 50% or less likelihood of reacting to a food are considered the optimal candidates for OFCs, especially during a follow-up of patients with a known food allergy who are being evaluated for development of tolerance (Table II).[14,23] Although this approach is not appropriate in many cases for an initial diagnosis, it selects the patients who have the best risk/benefit ratio of having a negative OFC and thus may be the optimal candidates for an OFC performed in the allergist's office.

These guidelines for deciding when to perform an OFC on the basis of the results of serum food-specific IgE and SPT are constantly evolving and need to be frequently updated according to new evidence (Table II).

TABLE I. Risk assessment for an OFC

Low risk of a reaction	High risk of a reaction	Low risk of a severe* reaction	High risk of a severe reaction
Recent accidental ingestion of a small amount of the food without clinical symptoms	Recent reaction to the food in the past 6-12 mo	No past severe reactions	Past severe reaction
		Food is not usually implicated in severe food-induced anaphylaxis (eg, meat, fruit, vegetable‡)	Severe reaction to trace amounts of food
			Food is frequently implicated in fatal and near-fatal food-induced anaphylaxis (eg, peanut, tree nuts, fish, shellfish, seeds)
Favorable test results† (see Table II)	Diagnostic or high-positive test results (see Table II)	No asthma	Asthma (regardless of severity)
			Conditions that may affect the resuscitation in case of severe food anaphylaxis: eg, cardiovascular disease, difficult vascular access or intubation, or β-blocker medication

*Severe reaction is defined as any lower respiratory or cardiovascular symptoms, or any 4 organ systems involved.[95]
†Laboratory cut-points for deferring OFC were defined for a few foods in children. These cut-points have not been evaluated in adults with food allergy.
‡It should be noted that any food is capable of inducing a severe anaphylactic reaction, including fruits and vegetables. The patient's previous reactions should be a guide for assessing the risk of a potential reaction during an OFC.

TABLE II. Tests to assess the likelihood of obtaining a positive or negative OFC in children

	Serum food-IgE (kIU/L)*		SPT wheal (mm)*	
Food	~95% Positive	~50% Negative†	~95% Positive	~50% Negative†
Cow's milk	≥15[16]	≤2[23]	≥8[21]	
	≥5 if younger than 1 year[132]			
Egg white	≥7[16]	≤2[23]	≥7[21]	≤3[22]
	≥2 if younger than 2 years[133]			
Peanut	≥14[16]	≤2 with and ≤5 without history of peanut reaction[24]	≥8[17,21]	≤3[17]
Fish	≥20[16]			

A subset of patients with undetectable serum food-specific IgE antibody and negative SPT has been reported to have objective reactions confirmed by OFC.[13]
*Phadia ImmunoCAP; SPT with commercial food extracts.
†In the authors' experience, children with about 50% chance of experiencing a negative challenge are the optimal candidates for an office-based OFC. However, serum levels of food-specific IgE antibodies and SPT wheal sizes are not absolute indications or contraindications to performing an OFC. Laboratory test results always have to be interpreted in the context of clinical history. For example, if a child had a recent anaphylactic reaction (past 6 mo) to a food, it is more prudent to defer an office OFC even if the test values are at 50% pass rate. In contrast, a child with peanut IgE of 20 kUA/L who recently tolerated an accidental ingestion of a product containing peanut butter may be a candidate for an OFC.

Clinical vignette

A 12-year-old child with history of generalized urticaria after ingestion of peanut at the age 5 years, who has a peanut IgE level of 17 kU_A/L (>95% PPV) and recently accidentally ingested 1 to 2 teaspoons of peanut butter without a reaction, may be a candidate for an OFC to test whether he has developed tolerance to peanut and can ingest a full serving without reactions. In contrast, a 12-year-old child with a peanut IgE level of 5 kU_A/L (approximately 50% PPV) and a recent (past 6 months) anaphylactic reaction (wheezing, urticaria, and emesis) to a small amount of peanut butter should not have an OFC to peanuts in the office despite the relatively low (50%) chance of reacting during the challenge predicted by the peanut IgE level.

TYPES OF OFC

There are various types of OFC that may be clinically indicated, including open, single-blind, or double-blind, placebo-controlled. The choice of the type of OFC is based on clinical assessment of the potential for bias in the interpretation of the results (Fig 1).[3,4,18,25]

Open OFC

Open OFC is an unmasked, unblinded feeding with a food in its natural form that is usually done if objective symptoms such as urticaria and wheezing are anticipated and concern for bias is low.[3] It is usually used for screening challenges in the office setting, according to a simplified protocol of gradual feeding with an age-appropriate serving of food, followed by an observation period of about 1 to 2 hours. It is simple to plan and reproduces the natural exposure in quantity and method of preparation. However, it has the highest potential for bias, which may depend on age, personality, and type of symptoms.[1,3,4,25,26] Whereas a clearly negative open OFC rules out reactions to the food, a positive result with only subjective symptoms, such as itchy mouth and nausea, may need to be confirmed by a blinded challenge.[3,4] Open OFC is a cost-efficient procedure that saves substantial time

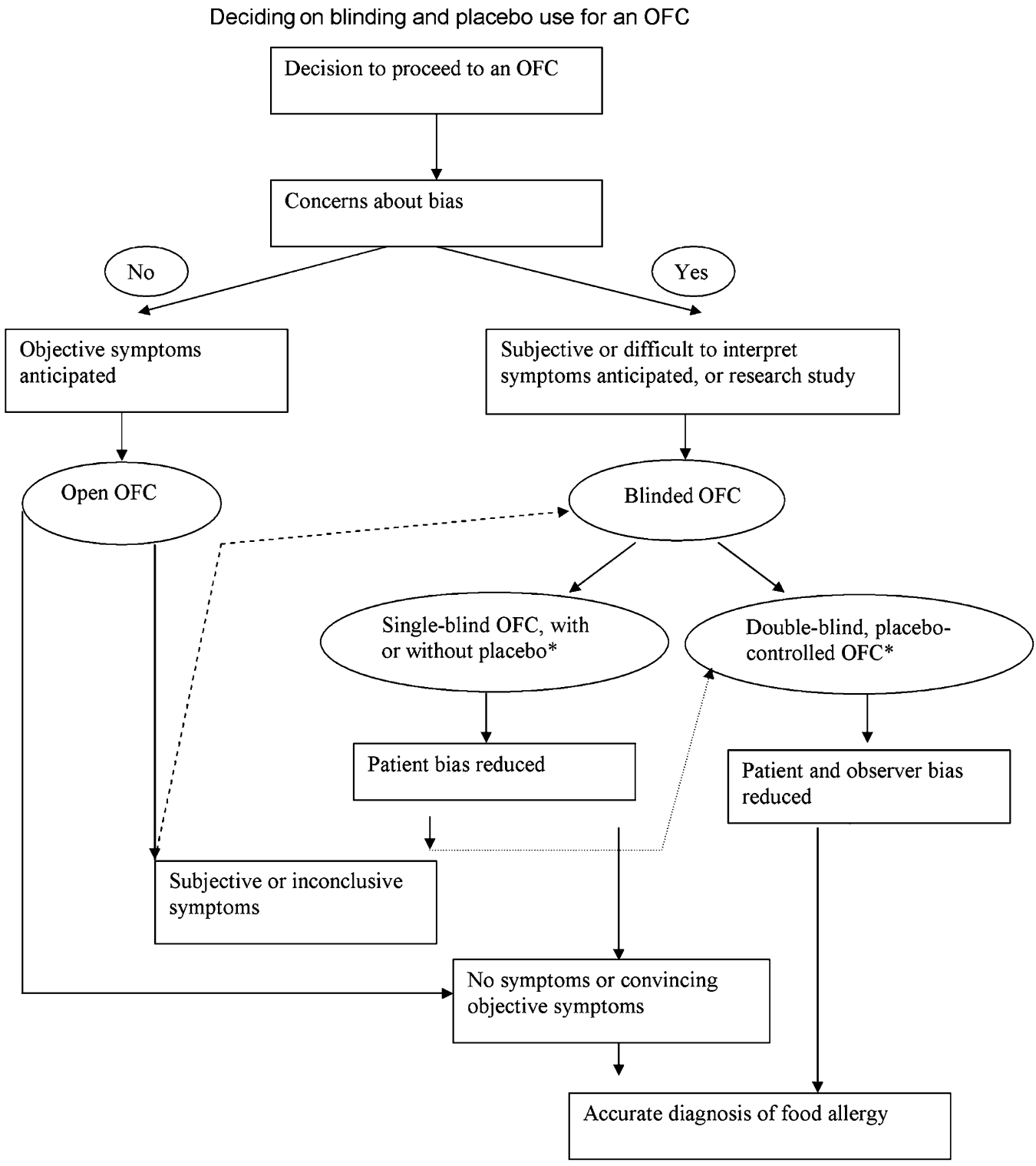


FIG 1. Decision process regarding selection of open vs blind OFCs. *Blinded portions of the OFC must always be followed by an open feeding with an age-appropriate serving of food in its natural form or the least cooked/baked/processed form of food that will be incorporated into the patient's diet at home.

and resources, particularly because only about one third of suspected foods result in a positive challenge.[4,27,28] It is thus considered a reasonable first choice to evaluate an adverse reaction to a food where the need for OFC has been established.

Open OFC can also be done using a slow dose-escalation schedule as outlined in the blinded OFC sections of this article. This may be a useful approach for OFC performed for clinical purposes when concern for bias is low but concern for a severe reaction is high.

Blinded OFC

Blinding and masking by mixing the challenge food with a masking vehicle or placing food in opaque capsules reduces bias. In the single-blind OFC, the observer but not the patient knows the food being tested. In the double-blind OFC, challenge material is provided by a third party, such as a dietitian, whereas the patient, the patient's family, and the observer are unaware of when the test food is given. Thus, bias is minimized. Placebo-controlled challenges may be administered in both single-blind and double-blind fashion.

Single-blind OFC

Single-blind OFC may be conducted with or without placebo, depending on the physician's judgment of the potential for subjective symptoms and the patient's anxiety. In the single-blind OFC without placebo, the patient is told that test food may or may not be served during the challenge; if 2 foods are tested on the same day, the sequence of the foods is not revealed to the patient. If the food is tolerated without any reaction or results in objective symptoms, valid conclusions can be drawn without the need for a placebo challenge. If multiple foods are being tested, the patient or parent is informed at the beginning that a series of tests will be carried out on several visits and that the tested foods will not be revealed until all challenges are completed. Single-blind OFC can be reliable in most cases evaluated in clinical practice; however, bias on the part of the patient may occur if the observer's attitude is inconsistent during all challenges. Single-blind OFC does not eliminate observer bias. In patients suspected of having a psychological response, the placebo might be tested first. If symptoms develop, foods that give a positive result should be retested for reproducibility in a DBPCFC.

If a placebo-controlled OFC is undertaken, the food should be administered in a form that would not allow its differentiation from the placebo.[3,4,8,26,29] A single-blind, placebo-controlled OFC consists of 2 sessions, 1 with active food and 1 with placebo, completed on 1 day with at least a 2-hour period separating the 2 sessions or on separate days. Alternatively, if such a prolonged challenge procedure is not practical but subjective symptoms are anticipated, placebo doses may be interspersed with real food doses during 1 session to help with the interpretation of vague, subjective symptoms. However, in dubious cases, and in patients presenting with subjective symptoms only, a protocol with repeated challenges should be applied by using 3 verum plus 2 or 3 placebo challenges.[30-32] For patients reporting delayed onset of symptoms, sessions of blinded OFC are separated by several days or weeks.[4,33-38]

After a negative blinded challenge, an open feeding with the tested food in its natural form should be undertaken approximately 2 hours after completing the final negative blind session or on a separate day, and followed by an additional observation period of 2 hours or less, depending on the clinical circumstances. These recommendations are based on the 3% possibility of detecting a reaction to an open feeding in children (no data available for adults),[24] possibly because of the larger amount of food ingested during an open feeding, effects of the vehicle matrix on allergen accessibility and absorption, or subclinical reactions caused by gradual administration.[39] Tolerance is proven when the food has been returned to the diet and consumed in its usual form of preparation and quantities.[3]

Double–blind, placebo-controlled OFC

A DBPCFC is the most rigorous challenge design for the diagnosis of adverse food reactions.[3,6] Test foods and placebo are prepared and coded by a third party not involved in evaluating the patient, minimizing both patient and observer bias. The sequence of sessions administering either the test food or the placebo is random. On completion of the challenges, the code is broken, and results are discussed with the patient or parent. With challenges to multiple foods, results are discussed after completing all the challenges. Open feedings with tested foods in their natural form should be done before concluding there is tolerance. DBPCFC is used for research studies and for selected cases in clinical practice.[3,4]

Challenges to multiple foods

For patients' convenience, open or single-blind challenges to more than 1 food may be done on the same day, separated by a break of approximately 2 hours, during which a light lunch may be consumed. If past reactions occurred later than 2 hours, multiple foods should not be tested on 1 day, unless there is a need to exclude immediate reactions in a patient who has a history of only delayed reactions to the test food, such as patients with allergic eosinophilic esophagitis who have positive SPT or detectable serum food-specific IgE. After a negative OFC, test foods should be reintroduced 1 at a time at home.

In the case of cross-reactive foods such as tree nuts, fish, or shellfish, challenging to multiple foods during 1 session might be considered for practical reasons, especially if patients have a low risk of reacting. Patients with a documented allergy to a food usually avoid all related foods. Patients allergic to 1 tree nut often choose to avoid all tree nuts without knowledge of their clinical reactivity because of the high risk of cross-contamination during commercial food processing. In a mixed food challenge, several nuts may be mixed together or ingested in sequence during 1 OFC session. If the patient reacts to the mixed food challenge, avoidance of all tested foods is recommended, or subsequent OFC to individual food may be conducted to identify the food allergens precisely. It is to be cautioned, however, that patients may not be able to ingest the recommended amount of each individual food during a mixed OFC. Considering these factors, several sessions of mixed challenges may be necessary to establish tolerance to all foods from the same food group (eg, all tree nuts) in both children and adults.

LOCATION OF OFC

Deciding where to perform an OFC should be based on risk assessment and capacity to treat anaphylactic reactions, and practical aspects such as preparation, administration, and monitoring. Low-risk challenges in cooperative patients are appropriate for the office setting. A physician may choose to perform higher-risk OFC in the office setting based on clinical judgment

and expertise, and the availability of materials and support for the treatment of a severe reaction.

The timing, type, and severity of expected symptoms may influence the selection of the OFC location. For subjective immediate symptoms that are not allergic in nature, such as behavioral reactions, the OFC may be done in the office while maintaining a behavior rating.[40,41] An OFC to confirm or refute delayed subjective symptoms may be undertaken in the office if follow-up is safe and reliable. If only a single dose is required for symptoms to occur, the patient receives the challenge at the clinic and is discharged but asked to return for evaluation should symptoms occur later. Logistics for challenges requiring multiple doses over multiple days are more difficult; however, the need for these types of challenges is infrequent.[4,24] Challenges to reproduce delayed, mild, objective symptoms such as skin rash may be handled in the office with the use of symptom diaries. Challenges for food protein–induced enterocolitis syndrome should be administered in a setting in which intravenous access can be secured and prolonged observation is possible because severe gastrointestinal reactions may occur hours after the challenge. Challenges that require exercise to precipitate symptoms need to be performed where suitable exercise equipment is available (see also Special Considerations for Administering an OFC).

In challenges with a greater likelihood for severe reactions, decisions to undertake an office-based OFC would have to consider availability of support staff, distance from the hospital, response time of emergency medical services, and office preparation (Table I). Otherwise, these OFCs are preferably conducted in a hospital in the inpatient, outpatient, or emergency department setting with close supervision and immediate availability of emergency treatment. When there is a very high risk for a severe reaction but OFC is required, challenges preferably should be done in the intensive care unit.

FOOD PREPARATION FOR OFC

The challenge food can be brought from home by the patient or parent for open office OFC, whereas for blind OFC, test material should be provided by a physician to ensure proper masking. The food should be prepared without cross-contamination or contact with other foods to which the patient may react and in a sanitary fashion. Preferably, single-ingredient foods should be used for OFC.

Special attention must be given to the form and degree of rawness of the food selected for an OFC. Thermal processing, heating, and cooking change protein conformation and may result in a change in allergenicity.[42] Patients who react to cow's milk, yogurt, or cheese may tolerate ingestion of milk baked into another product, such as a muffin. Similarly, subjects reactive to egg, such as a scrambled egg, may tolerate heated or baked goods containing eggs.[43-45] Preparation may affect allergenicity of beef, fish, shellfish, fruits, and vegetables implicated in the pollen-food allergy syndrome. Differences in the allergenicity of foods with different fat contents have been demonstrated.[28,46-54] During an OFC, 1 or several different forms of the food may be administered on the basis of the patient's history of clinical reactivity, taste preferences, and the form of the food encountered in the diet. The recommendation for eating a food after a negative OFC should reflect the manner in which the food was prepared during the OFC because tolerance to the cooked versions of many foods does not predict tolerance to the less cooked forms.

TABLE III. Suggested materials for preparing office-based blind OFCs

Vehicles	Spices, flavors
Capsule*	Sugar
Hamburger	Salt
Infant formula	Black pepper
Canned tuna fish	Corn syrup
Applesauce	Maple syrup
Ice cream	Mint flavor
Grape juice	
Popsicle	
Milk smoothie	
Lentil soup	
Chocolate pudding	
Mashed potato	
Oatmeal	
Fruit smoothie	
Tapioca fruit mixture cereal	
Amino acid–based elemental infant formula	

*Limitations associated with using capsules during an OFC: (1) it is difficult to administer adequate quantities of food; (2) using processed food, such as dehydrated food, may destroy relevant allergens; (3) patients may have difficulty swallowing large or multiple capsules; (4) early oral symptoms are bypassed; and (5) capsules may be more resistant to digestion, result in delayed absorption, and require long dosing intervals of 30 to 60 min and long observation periods of more than 2 h.

Challenge vehicles and masking for blind challenges

The original challenge vehicle chosen for blinding was opaque capsules.[1] These are very effective at hiding nearly any food, especially additives and spices, but have significant limitations: (1) it is difficult to administer adequate quantities of food; (2) using processed food, such as dehydrated food, may destroy relevant allergens; (3) patients may have difficulty swallowing large or multiple capsules; (4) early oral symptoms are bypassed; and (5) capsules may be more resistant to digestion, result in delayed absorption, and require longer dosing intervals of 30 to 60 minutes and longer observation periods of more than 2 hours. All these limiting factors should be taken into account when capsule use for blinding is considered.

Challenge foods may be mixed with various foods for masking to administer an adequate amount of the food in a natural form.[3,8] Limitations include (1) the need for creative approaches to selecting a masking vehicle (Table III), (2) the large volume of a challenge food, (3) the effects of food processing by cooking or baking, and (4) the food matrix effect.[54-56]

Vehicles are selected to mask the taste, odor, texture, and color of the challenge food. The selection of the vehicle is limited by patient preferences. Proper masking of the foods for blind challenges, particularly in research studies, may require professional tasters in a food laboratory designed for sensory testing and extensive dietitian support.[4,26,29] For most challenges in infants and young children, infant formulas and applesauce are convenient vehicles. Other vehicles used for masking purposes are fruit juices, oatmeal, puddings, potato pancakes, mashed potato, ground lean meat patties, and fruit smoothies. [8] In subjects reporting oral symptoms, gritty-textured and tart vehicles and placebos should be avoided to minimize false-positive reactions.[26,29] Flours of wheat, rye, oat, rice, barley, corn, potato, and soy; dried milk; and egg powders can be added to almost any food vehicle. Meats and fish can be masked in another tolerated ground meat.

TABLE IV. Oral challenges for food additives and spices

Food	Challenge substance	Placebo suggestions	Vehicles	Doses given at intervals of 20-30 min
Sulfites	Potassium metabisulfite	Powdered sucrose	Capsules	1, 5, 25, 50, 100, and 200 mg[134]
Preservatives, other	Sodium benzoate, butylated hydroxyanisole, butylated hydroxytoluene, parabens, sorbate, nitrites, nitrates	One preservative might be used as a placebo for another, lactose*	Opaque and dye-free capsules	1, 25, 50, 100, 200 mg[71]
Monosodium glutamate	Monosodium glutamate powder	Lactose,* microcrystalline cellulose, citrus drink	Capsules or citrus drink	200, 400, 800, 1600 mg[71] As much as 5 g[82,83]
Tartrazine (FD&C Yellow No. 5)	Tartrazine powder	Lactose*	Opaque capsules	Placebo, tartrazine 25 mg and 50 mg at 3-h intervals[84]
Dyes	Food coloring	Grape juice	Grape juice, capsules	1, 5, 10, 15 mg[71]
Aspartame	Aspartame	Lactose,* microcrystalline cellulose	Capsules	100, 200, 400, 800 mg[71] Maximum dose 150 mg[73]
Spices	Many different spices	Another spice	Mixed spices with ground poppy seed in applesauce, capsules	

*Lactose should not be used a placebo for patients with milk allergy or with lactose intolerance. Other placebo suggestions are as listed, such as microcrystalline cellulose.

Canned tuna fish, which is tolerated by most patients with fish allergy, can be used to mask the aroma of fish, provided tuna allergy has been ruled out.[53,57] It is preferable not to use fatty foods as vehicles because they can delay gastric emptying and intestinal absorption and result in a higher threshold dose and more severe symptoms in some patients.[54,55] Masking raw fruits or vegetables in the pollen-food allergy syndrome can be difficult because of the instability of the allergens. Birch Bet v 1–homologous plant food allergens are exquisitely sensitive to heating and to a lesser degree to other methods of processing,[26,29] such as freeze-drying.[48,52,58] Variety, ripeness of the fruit, and the storage method may influence the amount of the relevant allergen and confound the results of the challenge.[59-63] For clinical purposes, open OFCs with raw fruits and vegetables and cooked/processed counterparts to check for tolerance are usually sufficient. Research protocols for blinding OFCs to plant foods are published.[4,28,48,52,63-66]

Placebo

The placebo portion may be another food of a similar texture, look, smell, mouth feel, and taste to the challenge food and known to be tolerated by the individual.[3,4,8,26,29] When capsules are used, dextrose is an excellent placebo. For substances such as chocolate that make the capsule dark, carob is an effective choice.

Challenges to food additives

Allergic reactions to food additives, including preservatives, dyes, and colorings, occur in 1% of adults and as many as 2% of children, with a higher prevalence in atopic children, 2% to 7%.[67-72] Ingestion of sulfites such as sulfur dioxide, sodium and potassium metabisulfites, and bisulfites produces bronchoconstriction in as many as 5% of adults with asthma, especially if the asthma is unstable.[73] Skin prick testing may be helpful in screening for natural additives such as carmine, annatto, saffron, mannitol, and vegetable gums but is not reliable for synthetic additives.[74-80] A patient's response to a trial of an additive-free diet for a few weeks may help to support or exclude the need for an OFC.[71] Additive-free diets are highly influenced by the patient's expectations and are most helpful when patients report no response to an elimination diet because they exclude the need to perform an OFC. Oral challenges may be used to evaluate reactions to ingestion of food additives; however, the published protocols differ significantly[71,73,81-84] (Table IV).

DOSING SCHEDULE FOR OFC

Because the goal of an OFC is to test the patient's tolerance to a specific food in a quantity and form that will be subsequently encountered in the diet, the total quantity tested should approximate the regular, age-appropriate serving size of the food.

Total dose of OFC

In an OFC to diagnose immediate, IgE-mediated food hypersensitivity, the total challenge dose is administered in gradual increments to minimize the risk of severe allergic reaction and allow precise identification of the lowest provoking dose. In 1 approach, the total amount administered during a gradually escalating OFC equals 8 to 10 g of the dry food, 16 to 20 g meat or fish, and 100 mL wet food (ie, apple sauce).[8] The challenge food is mixed with the vehicle, and total amount/weight or volume is recorded, considered 100%, and administered in gradually increasing increments every 15 minutes. This time interval is chosen because most acute reactions occur within this time frame; the dosing interval must be adjusted on the basis of a patient's history.[4,85,86] Longer dosing intervals may be necessary for patients reporting reactions with delayed onset and may require the OFC to be carried out over several days.[36,87,88] (Box 2). After an asymptomatic gradually escalating OFC and/or if the patient is expected to tolerate the tested food, an age-appropriate serving (eg, 2-3 oz of fish or meat) of the food in its natural form may be served in small portions over a period of 30 to 60 minutes (Table V).

In non–IgE-mediated food protein–induced enterocolitis syndrome in which there is a low risk for immediate reactions, with symptoms usually starting within 1 to 4 hours after food ingestion, the entire portion of the challenge may be administered gradually in 3 feedings over a period of 45 minutes.[89-93] The total challenge dose is calculated as 0.15 to 0.3 g protein/kg body weight, not to exceed 3 g protein or 10 g whole food. In patients with a previous history of severe reactions, a lower starting dose of 0.06 g protein/kg body weight is recommended (Box 3). If the patient remains

BOX 2. An example of preparation for oral food challenge for IgE-mediated wheat allergy and calculation of doses consumed

1. Weigh* 10 g (2 teaspoons† = 10 mL) wheat flour.
2. Mix in 5 g (1 teaspoon = 5 mL) sugar.
3. Mix ingredients in applesauce for a total weight of 100‡ g (1/2 cup less 3 teaspoon or 115 mL).
4. Record timing, amount ingested, and any objective/subjective symptoms.

Cumulative dosing§:

Time (min)	% of total food	Amount of challenge food, g	Amount of wheat flour, g
00	0.1%	0.1	0.01
05	0.5%	0.5	0.05
20	1%	1	0.1
35	4%	4	0.4
50	10%	10	1
60	20%	20	2
70	20%	20	2
80	20%	20	2
90	24.4%	24.4	2.44
Total	100%	100 g	10 g

If challenge is stopped due to symptoms of an allergic reaction, calculate the dose ingested: challenge stopped after 55 g challenge food = 55% of the challenge food = 5.5 g wheat flour was consumed.

*A triple beam balance (approximately $67-$104) measures 100 mg accurately.

† Measurements in teaspoons and cups are provided for the practical purposes and case of preparing the food for an OFC in the allergist office, when establishing an exact threshold dose is not necessary.

*Measurements in teaspoons and cups are provided for the practical purposes and case of preparing the food for an OFC in the allergist's office, when establishing an exact threshold dose is not necessary.

‡The amount 100 g is used to simplify calculations. Total weight should be the smallest amount needed a that will mask the food and will be reasonable for the patient to costume at 1 sitting. The actual starting dose and dosing interval may vary depending on the patient situation.

Dosing increments may be different, such as doubling of the dose every 15-30 min until the maximum dose has been reached or the patient reacts, or an increment using logarithmic mean, such as 1, 3, 10, 30, 100, and so forth.[4]

Modified with permission from: Mofidi S, Bock SA, eds. A health professional's guide to food challenges. Fairfax (VA): Food Allergy and Anaphylaxis Network; 2004.[8]

TABLE V. Examples of portion sizes* for an open food challenge with common food allergens

Food	Portion size
Milk/dairy	6-8 oz milk or infant formula†
	½-1 cup yogurt
	½-1 cup cottage cheese
	½-1oz hard cheese
Soy/legumes	½-1 cup soy beverage
	½-1 cup tofu
	½-1 cup cooked beans (kidney, pinto, chickpeas, lentils)
Egg	1 slice of French toast‡ (1 egg per 1 slice of bread)
	1 hard boiled or scrambled egg
Grains (rice, corn, wheat, rye, barley, oat)	½-1 cup pasta‡/rice
	½-1 oz cereal
	½-1 slice bread
	½-1 muffin or roll bread‡
Meats	2-3 oz cooked lean meat/poultry
Fish	2-3 oz cooked fish
Shellfish	2-3 oz shellfish
Peanut	30 g peanut butter = 2 tablespoons peanut butter
Tree nuts	30-40 g crushed tree nuts = 25-30 pieces
Seeds	10-15 g seeds = 1-2 teaspoons seeds
Vegetables	½-1 cup cooked vegetable
	½-1 cup leafy raw vegetable
	1 small baked white or sweet potato or 70 g French fries
Fruits	½-1 cup raw/cooked/canned fruit
	½-1 small apple/banana/orange/pear
	6-8 oz fruit juice

*Depending on the age of the patient, adjustment of portion size is recommended.
†Preferred.
‡If a multi-ingredient food is used for the challenge, the patient should be tolerant to the food ingredients other than the one being challenged—for example, if French toast is used for an egg challenge, the patient should be tolerant to the bread ingredients. Alternatively, a form that is free of the other food allergens can be used, such as in a patient who has egg allergy and who is being challenged to wheat using pasta, egg-free wheat pasta should be used. It should be noted that the OFC should be performed with the least processed/cooked form of food that will be incorporated into patient's diet. In general, raw forms of foods are more allergenic than processed/cooked versions of foods; therefore, if the OFC was done with processed/cooked food (eg, hard-boiled egg) after a negative OFC, only similarly processed/cooked versions of food may be added to the patient's diet.

BOX 3. Food challenge preparation for food protein-induced enterocolitis syndrome

1. Obtain current weight of the patient.
2. Calculate the amount of food g protein/kg body weight; range 0.06-0.6, usual dosing 0.15-0.3 protein/kg body weight, up to a maximum of 10 g.
3. Mix the amount calculated with a vehicle of choice, such as rice milk.
4. Administer in 3 doses over 30-45 minutes

Example: The child's weight is 10 kg. Total dose of milk protein: 0.15 mg × 10 kg = 1.5 g = 42 mL skim milk = 1.4 oz skim milk (8 oz = 236.5 mL contains 8.4 g milk protein). Add 42 mL of skim milk to rice milk for a total volume 100 mL* and administer in 3 doses over a period of 30-45 min.

*100 mL is used to simplify calculations. Total amount of food should be the smallest amount needed that will mask the challenge food and will be reasonable for the patient.
Modified with permission from: A Health Professional's Guide to Food Challenges. Mofidi S and Bock SA, eds.[8]

TABLE VI. Approximate protein content in common foods and food forms used in OFCs

Food	Protein content in a serving	Challenge food form	Protein in 10 g challenge food
Egg, whole, cooked	1 egg = 6.1g	Egg, whole, dried	4.8 g
		Egg white, powder	7.5 g
Milk, skim	8 oz = 8.4 g	Milk, nonfat, dry	3.6 g
Milk, whole	8 oz = 8.0 g		
Peanut butter, generic, creamy	1 tablespoon (15 mL = 15 cc) = 4.6 g	Peanut flour, generic	5.25 g
Soy milk, generic	8 oz = 6.6 g	Soy flour, defatted	5.1 g
Isomil* soy formula	6 oz = 2.9 g	Isomil powder	1.3 g
Wheat bread, whole	1 slice (about 20 g) = 2.4 g	Wheat flour, whole grain	1.3 g

*Ross Laboratories, Abbott Nutrition, Columbus, Ohio.

asymptomatic for 4 hours, a second dose is given, generally an appropriate single-serving amount followed by 2 to 3 hours of observation.[94] Note that protein content varies widely among individual foods (Table VI).

Initial challenge dose

In challenges done solely for the purpose of patient care, the selection of an initial dose is guided mainly by clinical assessment of risk of reaction and type of food allergy (IgE versus non-IgE antibody-mediated). Gradually escalating open and blind OFCs to evaluate for immediate IgE-mediated food allergy are usually started with 0.1% to 1% total challenge food. If known, the initial OFC dose should be lower than the expected threshold dose—for example, the amount that the patient reacted to previously. Because for most foods, the content of allergenic protein is lower than the total amount of the challenge food, 0.1% is equal to approximately 1 to 5 mg food protein and to 8 to 10 mg of the whole food (Tables VI and VII). In an open OFC performed according to a simplified protocol, the entire serving of challenge food is usually divided into 3 equal portions.

The European Academy of Allergy and Clinical Immunology proposed initial doses of food for OFCs for the common food allergens[4]: peanut, 0.1 mg; milk, 0.1 mL; egg, 1 mg; cod, 5 mg; wheat, 100 mg; soy, 1 mg; shrimp, 5 mg; and hazelnut, 0.1 mg. These initial doses are lower than initial doses used in the authors' practices and impossible to measure without a precise scale, which is not a routine piece of equipment in the allergist's office (a triple-beam balance measures 100 mg accurately). Unless the patient is considered at risk for a severe reaction to a very small amount of food or the purpose of the OFC is to establish the threshold dose of food eliciting a clinical reaction, such low initial doses are not necessary.

A subset of patients with atopic dermatitis and the majority of patients with allergic eosinophilic gastroenteritis may develop delayed symptoms several hours to days after ingestion of a food. In patients with detectable food-specific IgE antibody, prolonged

TABLE VII. Eliciting doses for food challenge

Reference	Food	No. of patients, OFC type	Starting dose	Maximum dose	Eliciting dose	Comments
Hourihane, et al, 1997[33]	Peanut flour	14, DBPC	10 mcg peanut protein (21.63 mcg peanut flour)	50 mg peanut protein (108.15 mcg peanut flour)	8 subjects reacted; 3 had objective symptoms to 2,5, and 50 mg peanut protein; 5 had subjective symptoms to 5 mg (1 subject) and 50 mg (4 subjects) peanut protein	All 14 subjects had previously reacted during peanut OFC; in 50% of patients, the eliciting dose was comparable to contamination in consumer products
Wensing et al, 2002[35]	Hazelnut*	31, DBPC	1 mg hazelnut protein (6.4 mg hazelnut meal)	1000 mg hazelnut protein (6400 mg hazelnut meal)	1-100 mg hazelnut protein (6.4-640 mg hazelnut meal) for subjective reactions in 29 subjects;	
Taylor et al, 2002[128]†	Peanut‡	285, DB 73, DB or SB	Not specified	Not specified	1 mg and 1000 mg hazelnut protein (6.4 and 6400 mg hazelnut meal) for objective reaction in 2 subjects	
		6, SB			0.25 mg-125 mg peanut protein	
		100, open				
	Egg§	183, DB	Not specified	Not specified	0.13 mg-200 mg egg protein	
		8, DB or SB				
		18, SB				
		100, open				
		207, DB				
	Milk‖	6, SB	Not specified	Not specified	0.6 mg-150 mg milk protein	
		6, DB or SB				
		100, open				
		85, DB				
	Fish¶	4, SB or DB	Not specified	Not specified	1 mg-6000 mg minced fish	
		15, DB				
	Mustard#		Not specified	Not specified	(protein content unknown)	
Osterballe et al, 2003[135]	Egg**	56, DBPC	11 mg pasteurized whole egg	40 g pasteurized whole egg	0.3 mg protein (1 mg ground mustard seed)	No correlation among eliciting dose, age, and egg IgE
Hourihane et al, 2005[85]	Peanut††	40, DBPC	1 mg peanut protein	4 g peanut protein	Mean 3.7 g whole egg; range 11 mg-40 g	3 subjects reacted to 1 mg
Flinterman, et al, 2006[130]	Peanut††	22, DBPC	10 mcg defatted peanut flour (50% protein content)	3 g defatted peanut flour (50% protein content)	Median 36 mg (cumulative eliciting dose) ; range, 1-3936 mg peanut protein; 10 mg-3g for subjective symptoms; 100 mg-3 g for objective symptoms	No correlation between eliciting dose and history of reactions, SPT, or peanut IgE levels
Ballmer-Weber et al, 2007[136]	Soybean‡‡	30, DBPC	2 mg soy flour (55% protein content)	50 g soy flour (55% protein content)	10 mg-50 g soy flour for subjective symptoms; 454 mg-50 g soy flour for objective symptoms (cumulative eliciting dose)	A normal distribution statistical model predicted that 1% of patients with soy allergy would react subjectively and objectively to 0.21 and 37.2 mg soy protein
Leung et al, 2003[129]†	Peanut	82, DBPC	1 mg peanut flour	2 g peanut flour	Mean 330.9 mg peanut flour; range 1 mg-2 g for objective symptoms	

Unless specified, the eliciting dose reflects the actual dose given, not the cumulative eliciting dose.
DB, Double-blind; *DBPC,* double-blind, placebo-controlled; *SB,* single-blind.
*Hazelnut (raw dried hazelnut meal).
†Eliciting doses not specified for subjective vs objective symptoms.
‡Peanut (ground peanut, peanut flour, or peanut butter).
§Egg (egg white, dried egg white/whole egg, raw egg white, raw egg whole, cooked egg white.
‖Milk (nonfat dried milk, milk-based formula).
¶Fish (minced fish: cod, herring, plaice).
#Mustard (ground mustard seed).
**Egg (pasteurized, whole).
††Peanut (defatted peanut flour, 50% peanut protein).
‡‡Soybean flour.

challenges have been done. Initial doses of the food are administered in a gradual manner as DBPCFCs, under physician supervision, because of possible immediate IgE-mediated reactions. This is followed by subsequent feedings with regular portions of the food over the following days or weeks.[4,36-38] Patients may remain hospitalized or may record symptoms while continuing feedings at home.

Low initial challenge dose

The most sensitive patients may react at the first 10-mg to 100-mg dose of the challenge food, and in these patients, low-dose challenges should be considered. In addition, low initial dose is indicated when the OFC is performed to establish a threshold dose (eg, research study; Table VII). In published studies, as many as 50% of patients react to the initial dose of the challenge food,[4,24] and 11% of those reactions are severe.[24] Severe reactions, defined as any lower respiratory or cardiovascular symptoms, or any 4 organ systems involved, occur at a lower median dose of challenge than moderate and mild reactions.[95] The risk of a severe reaction is similar for all the foods studied, milk, egg, peanut, soy, and wheat,[95,96] and for any magnitude of SPT reaction and serum food-IgE value.[24,95]

In immediate, IgE-mediated food allergy, certain types of patients are a greater risk of severe reaction or anaphylaxis to OFC. These include individuals with a past history of food-induced anaphylaxis, subjects with persistent asthma, and patients with a history of reacting to trace food contaminants (Table II). High-risk patients should be challenged with a low initial dose.[4,86] In addition, allergists/immunologists conducting challenges in the clinic setting may consider a lower initial dose to minimize the risk of a severe reaction, even in a low-risk patient.

On the basis of a recently published consensus protocol to determine threshold doses, the OFC would begin at doses of 10 μg of the allergenic food and continue with doses of 100 μg and 1 mg followed by specified higher doses as large as 100 mg, administered at 30-minute intervals, until objective mild symptoms were elicited.[86] In the Europrevall protocol, the starting dose was set at 3 μg protein.[7] However, such low-dose OFCs are difficult to administer in the office because of difficulties with accurately measuring minute amounts of food and may be more suited for a specialized hospital or research facilities equipped to measure minute amounts of food. For instance, 1 mm^3 peanut butter, an amount that would fit on the head of a pin, equals approximately 250 μg peanut protein.

PREPARATION OF PATIENTS BEFORE OFC

Obtaining consent and discussing risks and benefits

Documentation of verbal or written informed consent should be considered. Before conducting a food challenge, outcome, risks, and benefits and the implications and the potential limitations of a negative or positive challenge should be discussed with patients and/or parents. The severity of the reaction during a positive OFC should not be used to estimate the severity of future reactions. Because OFC is stopped at the first objective symptom, an exposure to a larger amount of the food may result in more severe symptoms.[85] A negative challenge to a food from a group with high cross-reactivity such as tree nuts will allow the patient to eat this particular nut in isolation, preferably freshly cracked from the shell but not in mixes, chocolates, or snacks that may contain other nuts. After a negative challenge, patients are advised that regular ingestion of the food seems to promote continued tolerance and that there is a possibility of increased risk of recurrence of the allergy if the food, particularly peanuts, is not incorporated into the diet.[97-99] A recent survey reported that as much as a quarter of patients who had a negative physician-supervised OFC did not reintroduce the food into their diets.[100]

Patient preparation

Patients must be in good health, and their allergic diseases—asthma, allergic rhinitis, and atopic dermatitis—should be under optimal control at the time of the OFC to allow correct interpretation of the challenge outcome and to minimize the risk of a severe reaction.[1,4] Discontinuation of medications that may interfere with the OFC may be needed (Table VIII). In cases in which the challenge food is not associated with immediate allergic symptoms and has still been part of the patient's diet, it should be strictly eliminated for 2 weeks before the OFC. After elimination of the food for a prolonged period, reintroduction should be done under physician supervision because of the not infrequent occurrence of more generalized allergic reactions in patients who previously experienced only cutaneous symptoms of chronic eczema when a food is reintroduced after a period of strict elimination.[2,101,102]

Before the OFC, the patient should not eat for at least 4 hours for anticipated immediate reactions and for as long as 12 hours for anticipated late reactions. Fasting enhances the absorption of the challenge material and ensures that the challenge results are a result of the food administered rather than a food ingested in the previous hours. In infants and young children, who cannot fast for a long time, a light meal, half of their usual amount, can be administered 2 hours before the challenge. Starting the challenge at the patient's normal breakfast time will allow the challenge material plus vehicle to serve as a meal as the dosing progresses through the morning.

Patients should be advised that, in case of a significant reaction, they may need to remain under observation for several hours after resolution of symptoms. Parents should also be advised of the potential duration of the OFC and should be asked to make provisions to keep the child entertained during the lengthy office visit. This assures the child's continued cooperation with the OFC and removes subjective complaints.

ADMINISTERING AN OFC

The OFC should be conducted in a location where food may be heated and measured. A small food scale may be necessary for graduated challenges. To eliminate the risk of allergen cross-contamination, clean disposable plates, cups, utensils, and paper towels are used. The challenge area should be cleaned between challenges. For children, having familiar utensils and favorite cups and plates from home and creating a child-friendly environment can make the challenge experience more enjoyable and less anxiety-provoking. Selecting appropriate vehicles and placebos with alternatives, and having liquid and solid forms of challenge food readily available will avoid delays. Occupational/feeding therapy to increase acceptance of new textures and flavors may be necessary for young children with multiple food allergies who may refuse to try unfamiliar foods.

TABLE VIII. Guidelines for discontinuation* of medications that might interfere with interpretation of OFC

Medication†	Last dose before OFC
Oral antihistamines	3-10 d
Cetirizine	5-7 d
Diphenhydramine	3 d
Fexofenadine	3 d
Hydroxyzine	7-10 d
Loratadine	7 d
Antihistamine nose spray	12 h
Oral H2 receptor antagonist	12 h
Antidepressants	3 d-3 wk, drug-dependent and dose-dependent
Oral/intramuscular/intravenous steroids‡	3 d-2 wk
Leukotriene antagonist	24 h
Short-acting bronchodilator (albuterol, metaproterenol,	8 h
terbutaline, isoproterenol)	24 h
Long-acting bronchodilator (salmeterol, formoterol)	8 h
Inhaled cromolyn sodium	48 h
Nedocromil sodium	12 h
Theophylline (liquid)	24 h
Theophylline long-acting	48 h
Ipatropium bromide (inhaled/intranasal)	4-12 h depending on formulation and dosing
Oral/intranasal α-adrenergic agents	interval
Oral β-agonist	12 h
Oral long-acting β_2-agonist	24 h
Drugs that may be continued	
Antihistamine eye drops	
Inhaled/intranasal corticosteroids	
Topical steroids	
Topical immunosuppressive preparations: pimecrolimus, tacrolimus	

Based on references[137-139]:

*Risks of drug withdrawal should be considered and alternative treatments prescribed.

†Aspirin and other nonsteroidal anti-inflammatory agents and angiotensin-converting enzyme inhibitors should be avoided because of their theoretical ability to enhance or induce allergic reactions and potential interference with an OFC outcome interpretation.

‡This suggested guideline is based on the concern regarding the potential for suppression of the late-phase responses. In addition, the patient who received a short course of systemic corticosteroid may be going through an exacerbation that would either interfere with the OFC interpretation or potentially worsen the severity of a reaction. In patients who receive chronic therapy with systemic steroids, such as for inflammatory/rheumatologic diseases, risk/benefit ratio for stopping steroid therapy and substituting an alternative therapeutic agent vs performing an OFC while the patient remains on steroid should be evaluated on an individual basis.

Special considerations for administering an OFC

Although the majority of published food challenge studies have involved children, the procedure can be applied to adults.[51,103-108] Special attention should be given to factors that may influence challenge symptoms or conclusions. These include concomitant medications, level of physical activity at the time of the reported reaction, and ingestion of alcoholic beverages. Increased gastric pH, as occurs with antacids, histamine type 2–receptor blockers, and proton pump inhibitors, may be associated with decreased digestion of proteins and increased severity of reactions.[109-114] OFCs for food-dependent exercise-induced anaphylaxis are difficult to perform because there are no standardized protocols. A suggested protocol is treadmill exercise starting 30 minutes after food ingestion until a target heart rate for maximal exercise is reached or until onset of symptoms.[115-117] In these patients, increased intestinal permeability and activation of tissue transglutaminase with wheat ingestion were described.[118,119] Exercise OFCs are frequently negative, and sensitivity and specificity are unknown. However, in a few cases, exercise OFC has resulted in severe, life-threatening reactions.

Ingestion of aspirin and/or alcohol (ethanol) was reported to increase intestinal permeability and to augment reactions in the food-dependent, exercise-induced anaphylaxis.[120-122] In adult patients, it may be necessary to co-administer aspirin, alcohol, or antacid drugs during the challenge to reproduce the reaction.[4] In patients without such history, these drugs should be stopped before the OFC to avoid potential augmentation of the severity of the reactions. When specific foods cannot be identified on the basis of the patient's history, SPT, or serum food-specific IgE antibody test, an OFC with the entire meal that caused the reaction may be conducted.

MONITORING AND STOPPING OFC

Before starting the feeding, baseline vital signs—respiratory rate, heart rate, and blood pressure—should be recorded and physical findings should be documented to serve as a reference. Recording a peak flow and spirometry may be considered, especially for patients with asthma (Fig 2). Emergency medications must be readily accessible. For high-risk challenges, it may be prudent to have epinephrine drawn up and kept in the patient's room or in an immediately accessible location and with access to more elaborate emergency equipment or a crash cart. Alternatively, epinephrine auto-injectors may be used. An intravenous line may be considered, according to the physician's clinical judgment. Situations that may warrant insertion of an intravenous line are OFC in patients with (1) a past history of anaphylaxis or severe emesis (eg, food protein–induced enterocolitis syndrome), (2) patients with severe asthma who are judged to be at higher risk for food-induced anaphylaxis even in the absence of previous anaphylactic reactions, (3) difficult intravenous access, and (4) anticipated need for intravenous medications for resuscitation—for example, glucagon. The practice parameter for management of anaphylaxis suggests having an oxygen source, pulse oximeter to monitor oxygen saturation, sphygmomanometer, appropriate size nasal cannulas, masks, Ambubags, and oropharyngeal airways present or promptly available for treatment of anaphylaxis.[123] Throughout the OFC, the patient should remain under the supervision of a physician or a nurse with a supervising physician present in the office or in the hospital and promptly available. The patient should be re-examined before each dose is administered. Food residue on the lips, face, or hands should be wiped off with water to avoid contact irritation that may confound the interpretation of the OFC outcome. At the first symptom or sign of an allergic reaction, inspection of the skin and oropharynx and chest auscultation should be performed immediately. Vital signs should be measured including pulse, blood pressure, and oxygen saturation. The challenge should be stopped at any objective finding of an allergic reaction, and treatment should be initiated immediately. If there are respiratory symptoms, peak flow and/or spirometry should be obtained, if available, and compared with the baseline measurement, if one was obtained. However, pulmonary function may be normal in subjects having lower airway symptoms and increased airway hyperresponsiveness, documented with methacholine inhalation challenge, after a food

Example of an oral food challenge procedure form

PATIENT NAME_____**OFC DATE** _____

Benefits and risks of the oral food challenge were discussed with the patient / patient parent or guardian.
Physician's signature _____Date/time_____

Food to be challenged_____
Previous reactions to the challenge food No__Yes__ Date of most recent reaction_____
Symptoms_____
Route Ingestion__Contact__Inhalation__ Amount of food that caused the reaction_____
Time from ingestion/exposure to initial symptoms_____
Treatment received: Epinephrine__ Benadryl/Antihistamine__Other_____

H/o anaphylaxis to the challenge food No___ Yes____ If Yes: Date_____

Most recent test results Skin prick test (date)_____Serum food-IgE (date)_____

Other current food allergies_____

Allergy review of systems Asthma__AD__AR__Chronic urticaria__Latex allergy__Drug allergy_____

Current medications / doses_____
_____

Last dose of Antihistamine_____Beta-agonist_____Other_____

Last meal _____hours ago Challenge food avoided for _____weeks / months / years

Current illness Fever____URI____Wheezing____Other_____

BASELINE PHYSICAL EXAMINATION:

Vital signs Weight_____Height_____Heart rate___ /min Respiratory rate___/min BP_____mmHg
O_2saturation on room air %___ Peak flow_____ L/min
Spirometry FEV_1____(L), FEV_1____ % predicted FEV_1/FVC____ % predicted

Physical findings	Not done	Normal	Abnormal	Describe abnormal findings
General				
Skin				
HEENT				
Lungs				
Heart				
Abdomen				
Neurological				
Extremities				

EMERGENCY MEDICATIONS

Medication	Dose	Patient dose	Route
Epinephrine	0.01 ml/kg 1:1000 aqueous sol., max 0.5 ml		Intramuscular
Diphenhydramine	1.0-1.5 mg/kg, max 50 mg		Oral/IM/IV
Methylprednisolone	1-2 mg/kg, max 60 mg		IM/IV
Ranitidine	0.5 mg/kg, max 50 mg		Intravenous
Normal saline	10-15 ml/kg bolus, max 1000 ml /bolus*		Intravenous
Albuterol	2.5 mg in 3 ml normal saline		Nebulized

FIG 2. Template developed on the basis of Bock SA, Sampson HA, Atkins FM, et al. Double-blind, placebo-controlled food challenge (DBPCFC) as an office procedure: a manual. J Allergy Clin Immunol 1988;82:986-97;[3] and forms for the National Institutes of Health–sponsored Consortium of Food Allergy Research (U19 AI066738). *AD,* atopic dermatitis; *AR,* allergic rhinitis; *BP,* blood pressure; *FVC,* forced vital capacity; *HEENT,* head, eyes, ears, nose, and throat; *IM,* intramuscular injection; *IV,* intravenous injection; *sol,* solution; *URI,* upper respiratory infection. For complete guidelines for treatment of anaphylaxis, see Lieberman et al.[123]

challenge.[124] Therefore, a normal pulmonary function test in a patient experiencing respiratory symptoms should not be used as a criterion for ruling out a reaction during a food challenge. In case of subjective complaints, such as throat itching, mouth itching, skin itching, or nausea, a period of observation to allow for resolution of symptoms should be undertaken before administering a subsequent dose. In a single-blind OFC, administration of placebo food may help elucidate the significance of subjective symptoms. A challenge may be considered positive if subjective symptoms follow 3 doses of test food but not placebo food.[35] In nonverbal children, clues to the onset of a reaction may be subtle signs such as ear picking, tongue rubbing, putting a hand in the mouth, or neck scratching; or a changing in general demeanor, becoming quiet, becoming withdrawn, or assuming the fetal position. Similarly, isolated subjective symptoms in older patients, such as complaints of throat tightness or pruritus, nausea, abdominal pain, or general malaise, may represent a prodromal phase of a more severe reaction. A longer observation period before proceeding with a next dose or discontinuation of an OFC followed by treatment, depending on the level of the patient's discomfort and the physician's judgment, may be prudent. A flow sheet is recommended to record the doses administered, symptoms, signs, and physical findings as well as treatments during OFC[3] (Figs 3 and 4).

TREATING REACTIONS

In case of an allergic reaction to an OFC, treatment should be initiated promptly by the person administering the challenge, according to guidelines for anaphylaxis treatment.[125] Vital signs should be obtained as soon as symptoms are noted, but obtaining them should not delay treatment when the reaction appears to require rapid intervention or to be severe. Oral antihistamines are used to treat mild reactions; parenteral antihistamines can be administered via intramuscular or intravenous injection. In addition to intramuscular epinephrine, intravenous fluids are administered for treatment of immediate allergic reactions with hypotension and/or repetitive emesis. A recumbent position with elevated lower extremities to increase venous return to the heart is helpful for severe hypotension. An intravenous fluid bolus of 10 to 20 mL/kg is the first line treatment for a symptomatic food protein–induced enterocolitis syndrome challenge. Intravenous ranitidine can be administered in combination with diphenhydramine, but because of a slower onset of action, ranitidine should not be used without diphenhydramine in the treatment of anaphylaxis. Glucagon should be available for epinephrine-unresponsive reactors. Glucagon dosage is 1 to 5 mg infused intravenously over a period of 5 minutes, followed by an infusion of 5 to 15 μg/min titrated to clinical response. In children, the suggested dose is 20 to 30 μg/kg with a maximum of 1 mg.[123] Atropine may be necessary to treat bradycardia. Supplemental oxygen should be provided in case of hypoxia. Systemic steroids may be given for severe anaphylaxis, asthma, and significant generalized urticaria/angioedema, and for food protein–induced enterocolitis syndrome reactions, presumably to prevent late-phase responses, although there is no clear evidence to support such therapy. Vitals signs and physical examination should be repeated every 15 minutes or more frequently as needed for anaphylactic reactions until symptoms resolve and every 30 to 60 minutes after resolution until discharge. For challenges performed in an office setting, consideration should be given to transporting the patient to an emergency department or intensive care unit.

INTERPRETING THE OUTCOME AND POSTCHALLENGE CARE

Negative OFC

The OFC is negative if the patient tolerates the entire challenge, including the masked and open portions of a blinded OFC and observation period. The patient may be discharged home after at least 1 to 2 hours of observation for the immediate-type reactions and 4 hours for food protein–induced enterocolitis syndrome. Longer observation periods may be necessary in patients with later onset of symptoms in previous reactions, such as gastrointestinal complaints and/or eczema. Depending on the severity of the previous delayed reactions, observation may be warranted under physician supervision, or a patient may be discharged home and instructed to keep a log of symptoms over a period.

Positive OFC

In case of a positive OFC, the patient should remain under observation after symptoms have resolved with treatment for the duration based on clinical judgment, although 2 to 4 hours after resolution of symptoms for immediate hypersensitivity reactions and about 6 hours for food protein–induced enterocolitis syndrome are usually recommended. Patients who manifested mild symptoms such as a few hives that resolved promptly with or without treatment might be discharged after a 2-hour observation period after resolution of symptoms, if the physician supervising the OFC makes an assessment of a minimal risk of reaction progression. Patients with minimal residual symptoms such as a few new hives or swollen lips may be sent home after 4 hours, whereas a patient with a past history of a severe biphasic reaction should be observed for a longer period even in the absence of symptoms. Biphasic anaphylactic reactions to foods are reported in the literature, with symptoms starting as late as 6 hours.[126,127] Patients should be cautioned about the low potential risk of a reaction hours later and be provided with a means to contact the allergist/immunologist and an action plan.

Discharge instructions

All patients in whom immediate reactions are possible, regardless of the outcome of the challenge, should have an emergency treatment plan and medications available on discharge. After a negative challenge, the patient is advised to refrain from eating the challenge food until the following day because of the unlikely possibility of a delayed reaction to OFC. After a positive challenge with significant generalized cutaneous reactions such as urticaria/angioedema or a severe eczematous reaction, the patient should be advised about possible recurrent urticaria over a period of 1 to 2 days or an eczema flare persisting occasionally as long as several days. Long-acting oral antihistamine administered before discharge and/or on the following day and stepping up a topical regimen for eczema may be considered. Patients with immediate reactions may have loose stools or diarrhea over the period of the next 24 hours. The outcome of the OFC should be discussed with the patient and family before discharge. In case of a positive challenge, food avoidance should be reinforced, and recommendations for follow-up visits and evaluations within 6 to 12 months should be provided. Emergency treatment plans for allergic reactions, a prescription for a self-injectable epinephrine device, education regarding food avoidance, and dietary implications of food avoidance should be provided. For patients with severe reactions during the challenge, providing emergency medications

Example of an oral food challenge flow sheet

PATIENT NAME_____ Date_____

OFC type: Open _____Single blind _____Double-blind_____ Location: Office____ ED _____Inpatient_____
Food provided by: Patient___ Physician/dietitian___
Challenge food_____ Masking food_____ Placebo food_____
Total dose of challenge food_____ Total weight of challenge food mixed with masking food:_____

Time	Dose	Symptom score													
		Rash % body area	Pruritus	Urticaria	Rash	Sneezing /itching	Nasal congestion	Runny nose	Larynx	Wheeze	GI subjective	GI objective	Cardio-vascular	Total score	Comments stop/continue
Base	0														

Total dose ingested (%):_____ Time stopped:_____ Outcome: Passed__ Failed__

TREATMENT

Time	Symptoms	Treatment	Vital signs	Comment

Discharge home: Time _____Discharge instructions:_____
_____
Physician's signature _____Date/time_____

FIG 3. Template developed on the basis of Bock SA, Sampson HA, Atkins FM, et al. Double-blind, placebo-controlled food challenge (DBPCFC) as an office procedure: a manual. J Allergy Clin Immunol 1988;82:986-97[3]; and forms for the National Institutes of Health–sponsored Consortium of Food Allergy Research (U19 AI066738). *ED,* Emergency department; *GI,* gastrointestinal; *SBPCFC,* single-blind, placebo-controlled food challenge.

Oral food challenge symptom score sheet

Possible reactions

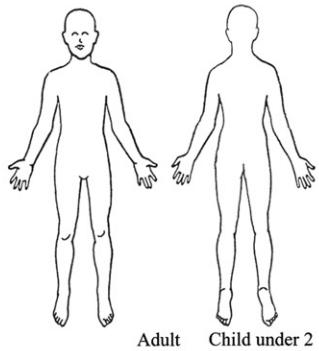
I. Skin

A. Erythematous rash: % area involved (see body surface area diagram)

B. Pruritus
0 = Absent
1 = Mild, occasional scratching
2 = Moderate: scratching continuously for > 2 minutes at a time
3 = Severe: hard continuous scratching

C. Urticaria / angioedema
0 = Absent
1 = Mild: less than 3 hives
2 = Moderate: more than 3 and less than 10 hives
3 = Severe: generalized involvement

D. Rash
0 = Absent
1 = Mild: few areas of faint erythema
2 = Moderate: areas of erythema, macular and raised rash
3 = Severe: generalized marked erythema (>50%), extensive raised lesion (>25%), vesiculation and / or piloerection



	Adult	Child under 2
Head	4.5%	8.5%
Neck	1%	
Anterior trunk	18%	18%
Posterior trunk	18%	18%
Leg	18%	14%
Arm	9%	9%

II. Upper respiratory

A. Sneezing/ Itching
0 = Absent
1 = Mild: rare bursts
2 = Moderate: bursts<10, intermittent rubbing of nose / eyes / external ear canals
3 = Severe: continuous rubbing of nose / eyes, periocular swelling and / or long bursts of sneezing

B. Nasal Congestion
0 = Absent
1 = Mild: some hindrance to breathing
2 = Moderate: nostrils feel blocked, breathing through mouth most of the time
3 = Severe: nostrils occluded

C. Rhinorrhea
0 = Absent
1 = Mild: occasional sniffling
2 = Moderate: frequent sniffling, requires tissues
3 = Severe: nose runs freely despite sniffling and tissues

D. Laryngeal
0 = Absent
1 = Mild: throat clearing, occasional cough
2 = Moderate: hoarseness, frequent dry cough
3 = Severe: inspiratory stridor

III. Lower respiratory

A. Wheezing
0 = Absent
1 = Mild: expiratory wheezing to auscultation
2 = Moderate: dyspnea, inspiratory and expiratory wheezing
3 = Severe: dyspnea, use of accessory muscles, audible wheezing

IV. Gastrointestinal

A. Subjective Complaints
0 = Absent
1 = Mild: itchy mouth, nausea, abdominal pain, no change in activity
2 = Moderate: frequent complaints of nausea or pain, decreased activity
3 = Severe: patient in bed; crying, notably distressed

B. Objective Complaints
0 = Absent
1 = Mild: 1 episode of emesis or diarrhea
2 = Moderate: 2-3 episodes of emesis or diarrhea or 1 of each
3 = Severe: >3 episodes of emesis or diarrhea or 2 of each

V. Cardiovascular

0 = Absent: normal heart rate and / or blood pressure for age or patient's baseline
1 = Mild: color change, subjective response (weak, dizzy), mental status change, tachycardia
2 = Moderate: drop in blood pressure >20% from baseline
3 = Severe: cardiovascular collapse, signs of impaired circulation, unconsciousness, bradycardia

FIG 4. Example of an OFC symptom score sheet. Modified from Bock SA, Sampson HA, Atkins FM, et al. Double-blind, placebo-controlled food challenge (DBPCFC) as an office procedure: a manual. J Allergy Clin Immunol 1988;82:986-97[3]; and forms for the National Institutes of Health–sponsored Consortium of Food Allergy Research (U19 AI066738).

on discharge should be considered. Information about the organizations that offer education and support should be given, such as the Food Allergy and Anaphylaxis Network (www.foodallergy.org) and the Food Allergy Initiative (www.foodallergyinitiative.org) and local support groups. In case of a negative OFC, instructions for food introduction into the diet should be provided. Regular ingestion of the food should be encouraged. The patient should be instructed to contact the office with any postchallenge issues such as delayed reactions or concerns about food introduction. The physician that conducted an OFC should make arrangements to provide follow-up.

OFC FOR RESEARCH

The following discussion is applicable to OFCs conducted for clinical research. As a result of scientific rigor, the majority of research studies use DBPCFC protocols, in which masking of challenge foods and development of placebo foods is provided by professional dietitians after extensive testing.[4,26,29] DBPCFC can be used to determine threshold doses for the food industry—for example, for assessment of product contamination with food allergens, for monitoring the accuracy of equipment cleaning procedures, and for studying the effects of novel future therapies for food allergy.[4,128,129] The threshold dose is defined as the lowest amount of the food that would elicit mild, objective symptoms, such as mild urticaria, erythema, or oral angioedema, in the most sensitive individuals. The threshold dose for a reaction varies by an order of magnitude among individuals and among foods (Table VII). Low-dose challenges may determine the amount of food that elicited no adverse reaction even among individuals with a high degree of sensitivity to that particular food. Reactions are not usually reported with less than 0.25 mg peanut protein, 0.13 mg egg protein, and 0.6 mg milk protein.[128] In a study of 22 children with peanut allergy, the level for no observed adverse effect was 2 mg peanut, which is equivalent to 1 mg defatted peanut flour.[130] In the case of a subjective reaction to a placebo portion of the OFC or subjective complaints to the challenge food, repeated blind placebo-controlled challenges should be performed. Two protocols based on statistical models using 3 active and 3 placebo challenges or either 3 active and 2 placebo challenges or vice versa reduced the likelihood of patients guessing the right sequence of challenge by chance from 50%, in the case of 1 active and 1 placebo session, to about 5%.[30-32] The frequency of placebo reactors must be considered in the analysis of the OFC outcomes in a cohort of patients because simply excluding the patients reacting to placebo will result in overestimating the frequency of true allergy.[131]

SUMMARY

The OFC is a valuable tool in the initial diagnosis and management of adverse food reactions including food allergy. *In vivo* and *in vitro* tests of food-specific IgE do not always correlate with clinical reactivity. OFC can be safely conducted under physician supervision, with appropriate precautions, although as noted throughout this article, the potential for serious reactions exists. Allergists/immunologists are particularly well qualified to conduct OFCs to assist patients with correct identification of foods causing adverse reactions. In appropriately selected patients, the potential risks, inconvenience, and expense are warranted by facilitating avoidance of unnecessary dietary restrictions and improving quality of life.

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